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# The renin–angiotensin system – a therapeutic target in COVID-19?

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## ABSTRACT

COVID-19, caused by infection with SARS-CoV-2, is a disease characterised by cough, fever and fatigue, which progresses to life-threatening lung injury in approximately 5% of patients. The SARS-CoV-2 virus enters the cell via ACE2. ACE2 is a component of the renin–angiotensin system (RAS) which has an important counterregulatory effect on the classical ACE-dependent pathway. Several antihypertensives increase ACE2 expression or activity, leading to concern that this may facilitate SARS-CoV-2 entry and worsen COVID-19 disease. However, ACE2 is protective against lung injury while ANG II (which is catabolised by ACE2) is associated with lung injury both in mice and humans. We propose that medications which inhibit the RAS ACE-dependent pathway may be beneficial in treating COVID-19 and should be explored in animal models and clinical trials. Here we give an overview of the RAS pathway with respect to COVID-19 and argue that strategies which manipulate this pathway might reduce the destructive lung manifestations of COVID-19 and improve patient outcomes.

**KEYWORDS:** RAS, Renin–angiotensin system, COVID-19, ACE2, lung injury

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## Introduction

SARS-CoV-2 is a novel coronavirus first identified at the end of 2019 as a cluster of pneumonias associated with exposure to a seafood wholesale market in Wuhan, China,<sup>1</sup> which has since spread around the world. The most common symptoms of the disease it causes, COVID-19, are fever, fatigue and a dry cough and it has a reported mortality rate of 4.3%.<sup>2</sup> The current COVID-19 pandemic arguably represents the greatest disease threat to the human population in a century. Urgent clinical studies are required to identify effective therapeutic strategies.

COVID-19 disease predominantly affects individuals with comorbidities, including hypertension (31.2% of hospitalised patients), cardiovascular disease and diabetes.<sup>2</sup> Patients with

## Key points

- > The renin–angiotensin system (RAS) has two pathways, the ACE-mediated vasoconstrictive side and the ACE2-mediated vasodilative side. Commonly used antihypertensives target the ACE-mediated pathway and indirectly promote the ACE2-mediated pathway.
- > ACE2 is the viral entry receptor for SARS-CoV-2 and its expression may be affected by RAS-blocking drugs. However, there is currently no evidence that these drugs enhance viral entry into cells and hence patients are advised to continue their usual antihypertensive medications.
- > Once COVID-19 infection has taken place, virus binding is likely to prevent ACE2 mediating its usual pneumoprotective effects. Hence drugs targeting the opposing ACE pathway may represent a potential therapeutic strategy in infected patients at risk of lung injury.

hypertension are more likely to require intensive care unit (ITU) care (58.3% of those who were admitted to ITU had hypertension compared to 21.6% of those who were not).<sup>2</sup> Because SARS-CoV-2 enters cells via interaction between its surface spike glycoprotein and the cell surface angiotensin converting enzyme 2 (ACE2),<sup>3</sup> there is interest in the possibility of using medications which affect the renin–angiotensin system (RAS), of which ACE2 is a major component.

## ACE2 and its role in COVID-19

The RAS is composed of two pathways. Both pathways begin with renin, which is produced by the kidney, converting angiotensinogen from the liver into angiotensin I (ANG I). In the first pathway, ANG I is converted to angiotensin II (ANG II) by angiotensin-converting enzyme (ACE). ANG II binds to its receptor, ANG II type 1 receptor (AT1R). This increases blood pressure by causing vasoconstriction and sodium retention. The second pathway is an ACE-independent pathway whereby a different enzyme, ACE2, converts ANG I to angiotensin-1-9 (ANG-1-9) and ANG II to ANG-1-7. ANG-1-7 interacts with two different receptors, Mas and ANG II type 2 (AT2R) receptor. This pathway works to oppose the actions of the ACE-dependent pathway by causing vasodilation, hence lowering blood pressure as well as having other cardioprotective effects.<sup>4</sup>

ACE2 is a transmembrane protein with a carboxymonopeptidase

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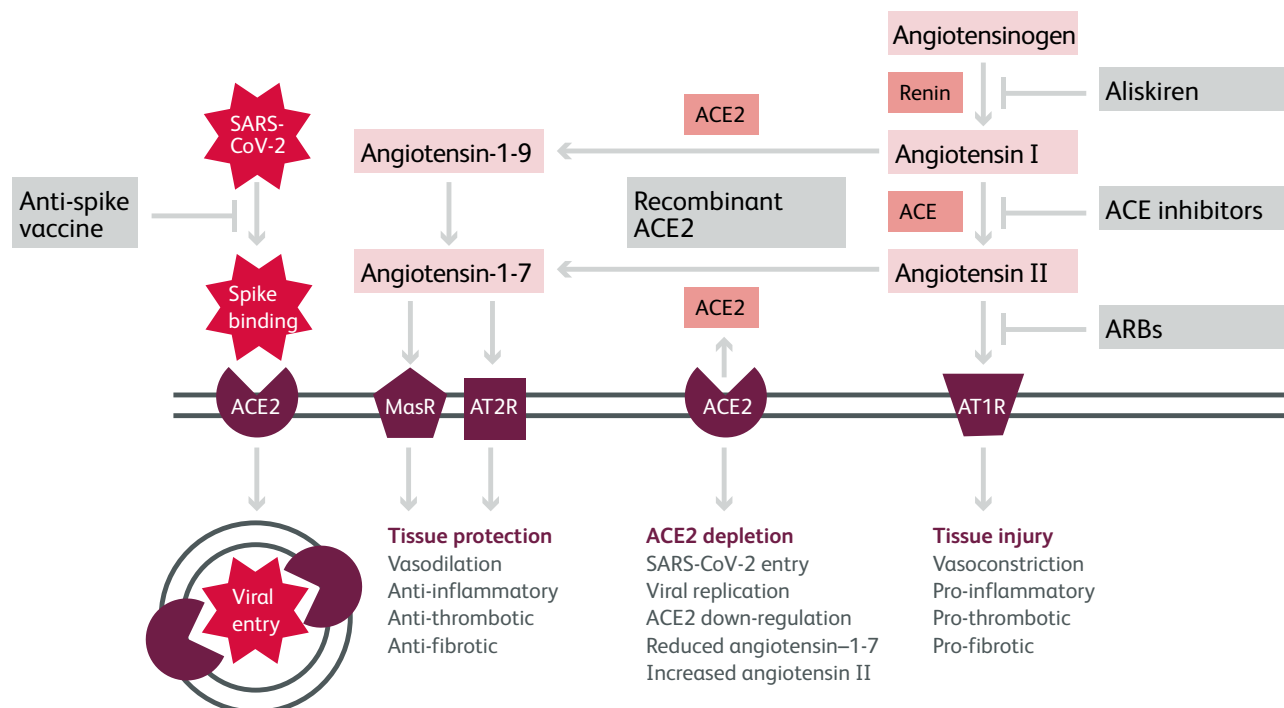
activity<sup>4</sup> and is an integral component of the second, ACE-independent, pathway. It is this protein which acts as the viral entry receptor for the recently identified SARS-CoV-2.<sup>3</sup> ACE2 is localised to lung alveolar epithelial cells, small intestine enterocytes, venous and arterial endothelial cells and arterial smooth muscle. Therefore the lungs, and potentially also the small intestine, are the likely sites of SARS-CoV-2 viral entry into the body and the sites of maximal cell infection.<sup>5</sup> This localisation of ACE2 has several implications for understanding the pathophysiology of the disease and could also be important for the development of certain treatments. Moreover, the expression of ACE2 in the lining of blood vessels is of note, as it could contribute to the risk of thrombotic events in patients with COVID-19, potentially via virion entry causing endothelial inflammation.<sup>6</sup> In addition, the interaction between ACE2 and the coronavirus virion could act as a target for vaccines. For example, a recent study characterising the receptor-binding domain of the viral spike protein, which interacts with ACE2, suggested that this protein could be used as a vaccine target which would prevent COVID-19 infection.<sup>7</sup> Interestingly, the ACE2 gene is carried on the X chromosome,<sup>8</sup> which may possibly account for the apparent increased susceptibility of men to COVID-19, compared to women.<sup>2</sup> This may be due to differential affinity of polymorphic variants of the ACE2 gene causing differential binding of SARS-CoV-2 and, hence, relative protection in heterozygous women compared with hemizygous men or, alternatively, due to functional haploinsufficiency in men and reduced ACE2 gene dosage.

### Antihypertensive drugs and COVID-19

As the RAS is integral to cardiac homeostasis and the control of blood pressure, drugs which interfere with the system are used as antihypertensives. Such medications include ACE inhibitors (ACEIs), such as lisinopril, and angiotensin II receptor blockers (ARBs), such

as losartan. While investigating the effects of RAS blockade on ACE2, which is not sensitive to blockade by ACEIs, Ferrario *et al* found that lisinopril and losartan alone increased expression of cardiac ACE2 mRNA in mice. Combined, these medications caused increased ACE2 activity but did not increase ACE2 mRNA expression. In addition, the ACEI increased plasma ANG-1-7 1.8-fold and decreased plasma ANG II. The ARB resulted in increased plasma levels of both ANG II and ANG-1-7 and increased cardiac ACE2 activity. ACEIs and ARBs therefore likely do not only lower blood pressure by inhibiting the first (ACE-dependent) pathway of RAS, but also by stimulating the second ACE2-dependent pathway, which has negative regulatory effects on the first pathway.<sup>9</sup>

Because SARS-CoV-2 enters the cell via ACE2, there was concern about the possibility of RAS-inhibiting drugs exacerbating COVID-19 infection by facilitating increased viral infection of cells, and this therefore raised the question of whether patients currently taking these drugs should stop or change them.<sup>10</sup> This was especially relevant as patients with comorbidities including hypertension, cardiovascular disease and diabetes are at greater risk of COVID-19, and may develop a more severe infection, potentially necessitating ITU intervention, and are also more likely to be taking these medications.<sup>2</sup> However, at present there is no evidence that the use of ACEIs or ARBs increases the risk of mortality in COVID-19 patients.<sup>11–13</sup> Although it can be argued that there is a hypothetical risk of increasing the number of cells infected by the virus in patients who take these medications, there needs to be a critical assessment of the risks of stopping them, such as increased risk of morbidity or mortality due to heart failure, hypertensive complications and worsening of chronic kidney disease.<sup>14,15</sup> On this basis, there is insufficient evidence to support abruptly stopping these medications in patients who take them in the community who are found to be positive for COVID-19. This conclusion is echoed by the European Society of Cardiology, who recommend that COVID-19 patients do not stop their ACEIs or ARBs.<sup>16</sup>



**Fig 1. COVID-19 and the renin-angiotensin system.** Diagram showing the dual ACE- and ACE2-dependent pathways and the potential for therapeutic interventions using RAS-inhibiting drugs, recombinant ACE2 and vaccine approaches.

## The role of RAS imbalance in lung injury: a therapeutic target?

Although RAS-inhibiting drugs merit caution given the above, there is also evidence to suggest that increased ACE2 expression may be beneficial in COVID-19 patients. SARS-CoV (a different coronavirus which caused the severe acute respiratory distress syndrome [SARS] outbreak in 2003) utilises the same receptor for viral entry and subsequently downregulates expression of ACE2 on the cell surface *in vitro*.<sup>17</sup> In addition, injection of the SARS spike protein in wild-type mice resulted in reduced lung function, whereas this effect was mitigated in ACE2-knockout mice, suggesting that the lung injury caused by the spike protein is dependent on modulating ACE2.<sup>17</sup> When Imai *et al* compared the effect of acid aspiration and sepsis (frequent causes of acute respiratory distress syndrome) in wild-type and ACE2 knockout mice, they found that the lung damage increased inflammation, bleeding and oedema to a greater extent in the knockout mice compared to wild type. Rescue experiments using injected recombinant human ACE2 protein decreased the severity of insult induced by lung injury. Similarly, they found that AT2R knockout mice had worsened insult-induced lung injury. This suggests that ACE2 and AT2R are pneumo-protective. Conversely, while they found that ACE, ANG II and AT1R promoted lung damage following a respiratory insult,<sup>18</sup> ACE2 protects against lung injury, likely by converting ANG I to ANG-1-9 and ANG II to ANG-1-7, leading to reduced levels of ANG II and reduced pneumo-damage mediated via AT1R binding.<sup>18</sup>

A recent study of 12 hospitalised COVID-19 patients compared their ANG II levels to healthy controls. They found that the ANG II levels in COVID-19 patients were significantly elevated compared to healthy controls. In addition, they found that the ANG II level was correlated with their viral load and lung injury.<sup>19</sup> Thus, there appears to be evidence for an imbalance of the RAS in the lungs of patients with COVID-19 which could explain the pathogenesis of the disease. This may be one of the mechanisms by which COVID-19 results in severe lung injury, the most common complication of the disease, affecting 61% of hospitalised patients.<sup>2</sup>

Although the obvious choice for a treatment for COVID-19 may be a compound with antiviral properties, we believe that there is strong evidence to support investigating the use of RAS-inhibiting drugs alongside antiviral strategies. The rationale here is that RAS-blocking drugs, which increase the activity of ACE2,<sup>9</sup> would reduce the levels of pneumo-damaging peptides, in particular ANG II. This should be explored urgently in animal models of the disease with a view to progressing to clinical trials in COVID-19 patients. Only then can we confirm the viability of this approach in reducing lung damage associated with SARS-CoV-2 infection. We suggest investigating the use of three different inhibitors of RAS.

We propose that direct inhibition of upstream renin with aliskiren might help to restore the angiotensin imbalance, triggered by SARS-CoV-2 cell entry, by preventing conversion of angiotensinogen to angiotensin I. Aliskiren, the only renin inhibitor approved for clinical use, has not featured significantly in discussions of RAS inhibitors in COVID-19, which has largely focused on the more commonly utilised ACEIs and ARBs instead. However, targeted inhibition of the initiating step of the RAS pathway may prevent downstream consequences caused by COVID-19-mediated loss of ACE2. An alternative approach is to use ACEIs with the aim of reducing levels of ANG II, which are high in COVID-19 patients,<sup>19</sup> and thereby increasing levels of ANG-1-9 and ANG-1-7.<sup>20</sup> Finally, ARBs, which are selective for the pneumo-damaging AT1R and not the pneumo-

protective AT2R,<sup>20</sup> might serve to help minimise downstream lung injury by blocking binding of ANG II to AT1R (Fig 1).

In support of this proposal, a recent observational study from China has shown that among hospitalised COVID-19 patients with hypertension, inpatient use of ACEIs/ARBs was associated with lower risk of all-cause mortality compared with ACEI/ARB non-users.<sup>13</sup> There might also be theoretical therapeutic benefit from combining the three different RAS inhibitor drugs in order to generate stepwise blockade of the RAS pathway and restore some balance of ANG I/II and ANG-1-7/-1-9. However, clinical trials of combination therapy in hypertension treatment, such as the ALTITUDE study, have resulted in excess adverse events<sup>21</sup> and therefore extreme caution would have to be applied.

## Conclusion

ACE2 is essential for the pathogenesis of SARS-CoV-2 by mediating viral entry. COVID-19 infection leads to ACE2 depletion, triggering an imbalance in RAS peptides, notably accumulation of ANG II and likely reduction of ANG-1-9 and ANG-1-7. RAS inhibitor drugs targeting the ACE side of the system, and hence increasing activity of the ACE2 pathway, have the potential to reduce COVID-19 associated lung damage and, if found to be safe and effective in animal studies, should be studied urgently in clinical trials of COVID-19 patients. These drugs are all immediately available and could potentially have a beneficial impact on mortality levels currently experienced in the COVID-19 pandemic. ■

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